Prognostic Significance of Exercise Versus Resting Blood Pressure in Hypertensive Men

Robert Fagard, Jan Staessen, Lutgarde Thijs, and Antoon Amery

The outcome of 143 male hypertensive patients, investigated in the period 1972–1982, was ascertained in 1989 to determine if brachial artery pressure measured during a progressive graded exercise test on the bicycle ergometer is a better predictor of mortality and cardiovascular events than pressure at rest. During the total follow-up time of 1,573 patient years, 27 patients suffered at least one fatal or nonfatal cardiovascular event and 13 patients died. Using the Cox regression model, the age-adjusted relative hazard rates of systolic pressure at supine rest, at 50 W, at peak work load, and at 50% of peak exercise capacity were significant for total mortality \((p \leq 0.01)\) and for cardiovascular events \((p \leq 0.03)\). Pressure during exercise, however, did not significantly \((p = 0.11–0.97)\) predict the outcome of the patients when age and pressure at rest were taken into account. The results were similar for diastolic pressure. In conclusion, intra-arterial pressures at rest and during submaximal and peak exercise significantly predict mortality and the incidence of cardiovascular events in hypertensive men, independent of age. However, there is no additional prognostic precision of the exercise pressures when age and the rest pressure are taken into account. (Hypertension 1991;17:574–578)

Hypertension is associated with increased mortality\(^1\) and a higher incidence of cardiovascular events such as myocardial infarction, angina pectoris, heart failure, cerebrovascular accident, transient ischemic attack, and intermittent claudication.\(^2\) In most epidemiological studies, casual blood pressure is measured. It is, however, possible that other measurements of blood pressure, such as pressure readings in basal conditions,\(^3\) during ambulation,\(^4\)-\(^6\) or during exercise,\(^7\) are better risk indicators. Because of the paucity of data on the prognostic significance of exercise pressure, we investigated whether pressures measured at submaximal and peak bicycle exercise contribute to the long-term prognosis of hypertensive patients, independent of the pressure measured at rest in the same conditions. Both total mortality and the incidence of cardiovascular events known to be associated with high blood pressure\(^2\) were considered during a mean follow-up of 11 years of 143 male hypertensive patients in whom intra-arterial pressure was measured at rest and during bicycle exercise in the period 1972–1982. In 1989, the vital status of all patients could be ascertained, and the occurrence of nonfatal events could be ascertained in all but one.

Methods

Study Population

The present analysis includes 143 male patients who were referred for the investigation of hypertension and who underwent invasive blood pressure measurements at rest and during exercise in the period 1972–1982. The routine investigation included history, clinical examination, appropriate laboratory tests, eye-fundus examination,\(^8\) electrocardiography, intravenous urography, and renal arteriography when indicated. All patients were in sinus rhythm and none had evidence of pulmonary disease. Patients had either never been treated for high blood pressure or had stopped their antihypertensive medication for at least 2 weeks. They gave informed consent after the nature of the procedures had been explained.

Exercise Protocol

The measurements were performed in the morning in the laboratory where room temperature was 18°–22°C. The brachial artery was punctured to measure intra-arterial pressure. The pressure was displayed on a Siemens Mingograph 81-recorder (Siemens Medical, Brussels, Belgium). Heart rate (beats/min) was determined from the electrocardiogram. Uptake
of oxygen (\(\text{VO}_2\)) and carbon dioxide output (\(\text{VCO}_2\)) were measured continuously by the open circuit method. Minute ventilation was determined by a pneumotachograph and oxygen and carbon dioxide concentrations by a paramagnetic and an infrared gas analyzer, respectively. The respiratory exchange ratio was calculated as \(\text{VCO}_2/\text{VO}_2\). A first set of measurements was obtained during supine rest, 30 minutes after termination of the technical procedure. The patients were then seated on the bicycle ergometer and the sitting rest measurements were performed 10 minutes later. A graded, uninterrupted exercise test was then started at a work load of 20 W for 4 minutes, and the load was increased by 30 W every 4 minutes until exhaustion.

Data at rest in the supine and in the sitting position, at 50 W (the highest work load performed by all subjects), and at the last work load were used for the analysis. Furthermore, arterial pressure was calculated at an exercise intensity corresponding to 50% of peak work load by use of the regression equation of pressure on work load for each individual patient. This represents data at a similar relative submaximal work load, in contrast to the data at the fixed work load of 50 W.

**Follow-up**

After the baseline examination, the patients were referred to their usual source of care. The vital status of the patients was determined in 1989 through contacts with municipal authorities. Causes of death were ascertained from contacts with physicians or family members, and from hospital files and autopsy reports if available. The health status of living patients was determined in the same year through comprehensive questionnaires, which could be filled in by the patients; if necessary, patients were contacted by telephone. In addition, the charts of patients followed at the University Hospitals in Leuven were checked for possible events. When cardiovascular events had occurred, the responsible physicians were contacted and all available documents concerning the events were checked. Events were coded according to the Ninth Revision of the International Classification of Diseases. The following events were considered: sudden death, myocardial infarction, cerebrovascular accident, heart failure, angina pectoris, transient ischemic attack, and intermittent claudication. All available information was checked, and objective evidence was required for acceptance.

**Statistical Analysis**

Data are reported as mean±SD. The survival analysis was performed by the Cox regression model.9,10 Two categories of end points were considered: 1) total mortality and 2) fatal and nonfatal cardiovascular events combined. In patients with more than one cardiovascular event, the first event was considered in the latter analysis. Relative hazard rates, with the 95% confidence limits, are reported for age and for blood pressure before and after adjustment for age. The relative hazard rate is an estimate of the effect on mortality or morbidity when the independent variable increases with one unit. For example, a relative hazard rate of 1.027 for resting systolic pressure indicates that a 1 mm Hg increase would be associated with an increase in morbidity or mortality of 2.7% throughout the observation period.

**Results**

**Characteristics of the Patients**

The characteristics of the patients at the time of the hemodynamic study are given in Table 1. Age ranged from 16 to 64 years. Blood pressure on admission to the hospital averaged 173/109 mm Hg. Eye-fundus examination, electrocardiography, and serum creatinine determination revealed no or only mild-to-moderate target organ damage in most patients. At entry into the study, previous cardiovascular complications had occurred in only two patients; they had experienced a cerebrovascular accident 2 and 7 years before the study but were not limited in their capacity to exercise. Five patients had a renal artery stenosis, which was considered significant in three. Ten patients had renal parenchymal disease and 128 were considered to have essential hypertension. Forty-eight patients had never been treated and 128 were considered to have essential hypertension, and 128 were considered to have essential hypertension.

Table 1. Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>143</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>35.3±12.0*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174±7.1*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.9±12.5*</td>
</tr>
<tr>
<td>Blood pressure on admission (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>173±28*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>109±20*</td>
</tr>
<tr>
<td>Duration of hypertension (months)</td>
<td>55 (1–384)†</td>
</tr>
<tr>
<td>Eye-fundus (Keith-Wagener; n) grade</td>
<td>53/54/28/3/5</td>
</tr>
<tr>
<td>Electrocardiogram (n)</td>
<td></td>
</tr>
<tr>
<td>SVT+RV, t&lt;3.5 mV</td>
<td>91</td>
</tr>
<tr>
<td>≥3.5 mV</td>
<td>52</td>
</tr>
<tr>
<td>T wave</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>115</td>
</tr>
<tr>
<td>Flat/negative</td>
<td>23</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>99.9±15.9*</td>
</tr>
</tbody>
</table>

n, number of patients.
*Values are mean±SD.
†Values are means (range).
Blood Pressure at Rest and During Exercise

Systolic and diastolic pressures averaged 157±25/86±16 mm Hg after 30 minutes of supine rest, 186±32/98±18 mm Hg at 50 W, and 214±37/102±21 mm Hg at the last work load. Heart rate averaged 78±14, 108±17, and 172±24 beats/min, respectively. Peak oxygen uptake was 2.24±0.60 l/min, and the highest respiratory gas exchange ratio was 1.06±0.11.

Total Mortality

The vital status in 1989 was known in all 143 patients. The average time of follow-up (until death or until the date of the last available information in 1989) was 11 years, and the total follow-up time was 1,573 patient years; the longest follow-up was 17 years. Thirteen patients died an average of 4.3 (range, 0.7–12) years after the hemodynamic study. The survival curve is given in Figure 1. Mean age at the time of death was 48 (37–65) years. The cause of death was sudden death in six patients: two were found dead in bed, two died while driving, and two deaths were witnessed at home. Two patients died of myocardial infarction, which was confirmed by autopsy in one patient and after admission to hospital in the other. Myocardial infarction was the probable cause of death in one patient, who died shortly after severe chest pain. Two patients died of a cerebrovascular accident and one of diabetic coma. One death was accidental; this patient was successfully resuscitated after a myocardial infarction 1 year before.

Total mortality was significantly related to age (relative hazard rate, 1.056 [1.009–1.105]; p=0.02), to systolic blood pressure at supine rest (rate, 1.029 [1.009–1.050]; p=0.005), and to diastolic pressure at rest (rate, 1.041 [1.004–1.080]; p=0.03). Table 2 summarizes the age-adjusted relative hazard rates of blood pressure for total mortality. The relative hazard rate of systolic brachial artery pressure was between 1.021 and 1.027 and was significant at all levels of activity. This rate ranged from 1.025 to 1.041 for diastolic pressure and was significant, except for pressure at sitting rest. When age and resting pressure were forced into the equation, the relative hazard rates for systolic and diastolic pressures were not significant at 50 W (p=0.16 and 0.76, respectively), at 50% of peak work load (p=0.38 and 0.67), or at peak work load (p=0.11 and 0.32). The various relative hazard rates were independent of smoking habits and serum cholesterol concentration.

Cardiovascular Events

The 1989 health status could be ascertained in 142 of the 143 patients. The first occurring cardiovascular events included eight deaths (sudden death, four; myocardial infarction, two; cerebrovascular accident, two). The five nonfatal myocardial infarctions and the three nonfatal cerebrovascular accidents were documented in hospital. Of the seven patients with angina pectoris as the first event, coronary angiography was performed in five, and all had significant coronary artery lesions; in two others, ischemic electrocardiographic changes were observed during chest pain at rest or during exercise testing. In patients with intermittent claudication, peripheral occlusive arterial disease was retained on the basis of arteriography and subsequent surgery in one patient and of nonpalpable foot arteries in two. One patient suffered a transient ischemic attack, and atheromatous lesions of the carotid artery were found on angiography.
The crude relative hazard rates were 1.026 (1.016-1.037; \( p=0.001 \)) and 1.032 (1.006-1.058; \( p=0.02 \)) for systolic and diastolic pressures at rest, respectively. The age-adjusted relative hazard rates (Table 3) were significant at the various levels of activity, except for sitting diastolic pressure. When age and resting pressure were forced into the equation, the relative hazard rates for systolic and diastolic pressures were not significant at 50 W (\( p=0.94 \) and 0.78, respectively), at 50% of peak work load (\( p=0.97 \) and 0.98), or at peak work load (\( p=0.16 \) and 0.62). The various relative hazard rates were independent of smoking habits and serum cholesterol levels.

### Discussion

The level of blood pressure is related to cardiovascular morbidity and mortality. However, there is still debate as to which blood pressure is best related to the complications of hypertension. The purpose of the present study was to determine if blood pressure measured during exercise adds prognostic precision to the blood pressure measured at rest in the same standardized conditions. In 1989, we determined the outcome of 143 male patients who were investigated for hypertension in the period 1972-1982, and in whom intraarterial pressure was measured at rest and during a graded exercise test up to exhaustion. Ninety percent of the patients had essential hypertension. One third had never been treated for hypertension, and the rest were untreated for an average of 4.4 weeks before the investigation. Because only men were studied, it is not certain if the results also apply to women.

Thirteen patients died, mostly from cardiovascular causes, during the total follow-up time of 1,573 patient years. The death rate was 8.3 deaths/1,000 patient years. The patients died at a relatively young age, 48 years on average. Total mortality was significantly related to age and to blood pressure at rest; the latter relation persisted after adjustment for age. This is in agreement with observations of Bulpitt et al.,\(^{11}\) who prospectively studied pretreatment factors predicting death in hypertensive patients followed up at hospital hypertension clinics or in general practice. Exercise pressures were considered at 50 W, which was the highest work load performed by all patients, at the last work load, and at 50% of maximal capacity. The age-adjusted relative hazard rates of systolic and diastolic pressures at rest and at these three levels of exercise were similar. In a further step of the analysis, it was found that exercise blood pressure did not contribute to total mortality, independent of pressure at rest.

In the analysis of cardiovascular events, fatal and nonfatal cardiovascular events known to be associated with blood pressure in large prospective epidemiological studies\(^ {2}\) were considered, that is, sudden death, myocardial infarction, angina pectoris, cerebrovascular accident, transient ischemic attack, and intermittent claudication; heart failure was not observed. All available information was checked and objective evidence was required for acceptance. Twenty-seven patients had experienced such an event as the first event in the course of follow-up. Age was a significant predictor. The age-adjusted relative hazard rates of arterial pressure were significant at the various levels of activity, except for sitting diastolic pressure. There was no additional prognostic precision of exercise pressures at the various levels of activity, when age and pressure at rest were taken into account.

Our results are at variance with data by Gosse et al.,\(^ {7}\) who suggested that blood pressure measured at maximal exercise is a better prognostic indicator than clinic pressure. However, in the latter study half of the patients were on antihypertensive treatment at the baseline examination and outcome could not be traced in 19% of the patients. In addition, the authors only reported on blood pressure measured at maximal exercise. Pressure was measured noninvasively, and therefore could be different from intra-arterial pressure.\(^ {12}\) The comparison was not strictly between exercise and rest pressure, but between pressure measured during a standardized exercise test and in nonstandardized clinic conditions, which could have favored exercise pressure. Finally, discriminant analysis is less appropriate than the Cox regression model for this type of analysis, and using this statistical method, it was not proven that exercise pressure is a significantly better prognostic indicator than clinic pressure.\(^ {7}\) These authors\(^ {13}\) also observed that left ventricular mass was somewhat better related to systolic pressure at the end.
of exercise than to clinic pressure but did not report whether this difference was significant. More recent studies\textsuperscript{14-16} reported similar associations of indexes of left ventricular hypertrophy, assessed by echocardiography or electrocardiography, and blood pressure during exercise and at rest in hypertensive patients. Others observed significant correlations of left ventricular mass with exercise blood pressure\textsuperscript{17-19} but not with pressure at rest; the latter finding is in contrast with the general finding of a significant relation between left ventricular mass and resting systolic pressure.\textsuperscript{14-16,20-23} Furthermore, exercise intra-arterial pressure was not better related to eye-fundus grade than pressure at rest.\textsuperscript{14}

Our findings do not, however, exclude that blood pressure during habitual daily activity could be a better predictor than pressure at rest. Perloff and coworkers\textsuperscript{5,6} did indeed demonstrate that the incidence of cardiovascular complications was greater among patients with higher ambulatory blood pressure than predicted from office blood pressure measurements. Mann et al\textsuperscript{6} found that 24-hour intra-arterial readings added prognostic precision to the clinic value. Similarly, the association of target organ damage was significantly better\textsuperscript{21-24} or tended to be better\textsuperscript{20,22,23} with ambulatory blood pressure than with casual or clinic pressure.

In conclusion, the present study demonstrates that intra-arterial pressure during well-standardized exercise testing does not add to the prediction of total mortality and cardiovascular events in hypertensive men when age and resting pressure are taken into account. These data suggest that measuring blood pressure during standardized exercise has only a limited value in the prognostic evaluation of hypertensive men.

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References


Key Words • blood pressure • cardiovascular events • exercise • essential hypertension • mortality • prognosis
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